Principles of Vaccination

The art and science of your vaccination practice is complicated, and is getting more complicated by the day. New vaccines are introduced and need to be integrated into the series. Older vaccines are removed from the market or recommendations for their use are changed. Throw in a new combination vaccine or two, and it's easy to get confused. We have found that a discussion of general principles of vaccination, and broad recommendations for the use of vaccines can help reduce this confusion. So we will spend most of today's program discussing these general principles and recommendations. We will then apply the general principles to specific vaccines in subsequent sessions. We think this will make your complicated task a little easier.

Any discussion of immunization should begin with a discussion of immunology. We do not intend to go into much detail, but we will give you enough to get the general idea. If you would like to follow along in your book, this information is in Chapter 1. Most of our slide panels are in the margins of the pages, so you should not have to take many notes.

Let's start off with a consideration of immunity. What is it exactly? In the broadest sense, immunity is our ability to recognize **self from nonself**. That is, the immune system is able to recognize and eliminate foreign, or nonself material, from the body, and leave everything that belongs there alone. But for the purposes of this program, we will use a narrower concept of immunity. You can think of immunity as **protection from infectious disease**, the ability to recognize and eliminate infectious agents, such as viruses and bacteria, and to prevent infection with these agents in the future.

There are two basic types of immunity, active and passive. It's possible for both types to be present simultaneously. We will discus both types of immunity, starting with active immunity. Active immunity is the best type, because it is **protection produced by a person's own immune system**. Active immunity is **usually permanent**, and provides long lasting protection against reinfection with that virus or bacteria.

A good model for active immunity is that which occurs after an infectious disease. In most cases, lifelong immunity results if a person survives an infectious disease. Second infections- at least symptomatic infections- are not common in an immune person. This is sometimes called NATURAL immunity, although there is nothing natural about an infectious disease.

To illustrate the mechanism of naturally acquired immunity, we have prepared a short animation of the process. Have a look.

The first event leading to immunity is exposure of a susceptible person to an infectious agent, in this case, a virus. Because the person is not immune the virus is able to replicate, and spreads throughout the body. As virus spreads, some are captured by macrophages or antigen presenting cells. Each macrophage phagocytizes, or literally eats the virus, disassembles it and presents some of the viral parts on its surface. The viral antigens presented by the macrophage attract two key cells of the immune system: a t-cell shown in yellow, and a B-cell, shown in blue. The T-cell controls many functions of the immune system. It sends chemical signals to activate the B-cell. Each activated B-cell then begins to divide. This process is known as clonal expansion, because each daughter B-cell is a clone, identical to the original activated cell. Each of these millions of B-cells begins to produce protein molecules called antibodies. Antibodies attach to the invading virus and destroy it. The combined forces of the antibodies and other components of the immune system eliminate the invading virus from the body. The antibodies remain after the virus has been eliminated, making the person immune to that virus. Immunity will persist for years, probably for the life of the person. The entire process from infection to elimination of virus usually takes three to four weeks, but it can take longer, depending on the organism. Months or years later, another exposure to the virus may occur. The antibodies will immediately attack, and the virus will be unable to replicate enough to cause disease. The exposed person is usually unaware that the exposure even occurred.

What was illustrated in that animation is generically known as an immune response. There are two central elements in this immune response to infection-antigen and antibody. Antigen is a **live or inactivated substance, such as a protein or polysaccharide, which is capable of producing an immune response**. The antigen in the animation was the invading virus. Antibodies are the muscle of the immune response. Antibodies are **protein molecules, known as immunoglobulins, produced by B lymphocytes** in response to the antigen. Antibodies assist other components of the immune system in the **elimination of the antigen**. Antibodies are very specific, and only recognize the antigen which produced them, or very closely related antigens.

The immune system is complex, and there are other components which help control invasion by infectious agents. There is another arm of the immune system known as cell mediated immunity, which involves activated T lymphocytes or killer cells. But for simplicity, we will equate the presence of antibody with a person being immune, or protected from that disease. There are exceptions to this, such as pertussis, which we will discuss later in the course.

So antibodies are great things to have around. It’s preferable to actively produce the antibodies yourself, but it is not the only way to get them. It is possible to get them, ready made, from another person. The transfer of antibody from one person to another is known as passive immunity. The antibodies still do what they are supposed to do -- attack and help eliminate antigen. This type of immunity is usually effective, at least for a while. The problem is that passive

immunity is not permanent. To illustrate passive immunity, have a look at this second animation.

One type of immunity is passive immunity. With passive immunity, a person receives antibodies from another person, rather than producing them. The most common type of passive immunity occurs when a fetus receives its mother's antibodies across the placenta. A full-term baby is born with antibodies against the same diseases to which the mother is immune. As the infant grows, the maternally acquired antibodies circulate through the body, waning slightly with time. If the child is exposed to a disease for which it has a maternally acquired antibody, the antibody will attach to and destroy the invading organism, just as it would if the child were naturally immune. One potential problem with passive immunity is that the antibodies cannot tell the difference between disease virus and live vaccines. Therefore, if the child gets a live vaccine immunization while it still has circulating antibody, the antibody will attack and destroy the vaccine, preventing active immunity from occurring. Eventually, by the time the baby is about a year old, all maternal antibody will have disappeared. Now the child is susceptible to infection. Because there is no antibody, live vaccines given to the child will confer active immunity. Maternally acquired immunity is only one type of passive immunity. Injection with immune globulin or disease-specific globulin or blood transfusion are other ways of conferring passive immunity. But passive immunity, no matter how acquired, is always temporary. Active immunity, either natural or through vaccination, is the only way to become permanently immune to disease.

Passive immunity is defined as protection in the form of antibody transferred from an exogenous source, usually another person. Transplacental antibody is a very important source of passive immunity. Maternal antibody is actively transported across the placenta in the last six to eight weeks of pregnancy. So a full term infant is born with the same antibodies that the mother has. The down side is that if the mother is not immune to a disease, the infant will not be either, and is susceptible to infection from the moment of birth. Passive antibody transfer happens in other ways, of course. Some antibody is passively transferred with blood transfusions, for example.

There are three chief medical sources of passive antibody. The first is **homologous- meaning same species- pooled human antibody, commonly known as immune globulin**. Those little vials of immune globulin contain antibody from the blood of hundreds of American adult donors.

Immune globulin is used for hepatitis A and measles postexposure prophylaxis, among other indications. American donors can be used to produce this because most adults in the U.S. have antibodies to these viruses. In contrast, immune globulin from the U.S. would have little or no antibody to yellow fever, since few North Americans are exposed to this disease or vaccinated against it. A second antibody product is **homologous human hyperimmune globulin**. These products have high concentrations of antibody to a specific disease. For instance hepatitis B immune globulin, HBIG, which is used for postexposure prophylaxis,

is taken from donors with high levels of hepatitis B antibody. HBIG will contain a large amount of hepatitis B antibody, but also smaller amounts of antibodies to other antigens, like measles and hepatitis A. Hyperimmune globulin products are also available for postexposure prophylaxis of tetanus, varicella, and rabies. Vaccinia immune globulin is used to treat certain adverse reactions following smallpox vaccine.

There are also two antibody products available for the prevention of respiratory syncytial virus- or RSV- infection in infants. There has been a lot of confusion about these products. Although they are used to PREVENT RSV infection, they both contain ANTIBODY. They are NOT vaccines. One product is called **RSV-IGIV. It's a human** hyperimmune globulin, and is administered intravenously. It is like other hyperimmune globulin products, and in addition to RSV antibody **contains antibody to other antigens**. The second is called **palivizumab, or Synagis**. Synagis is also antibody, but it is given by intramuscular injection. Synagis is unique because it is **monoclonal** – it is produced in a special way so that it **contains ONLY RSV antibody**. It does not contain antibody to any other antigen. We will discuss the implications of this a little later when we talk about antibody vaccine interactions.

A third antibody product is **heterologous -- meaning different species -- hyperimmune serum**, also known as antitoxin. Antitoxin is different because it's produced in horses, not humans. Equine antitoxin is used in the United States for diphtheria and botulism treatment, and for treatment of some snake bites. The problem with equine antitoxin is that the immune system may see the horse protein as not self and develop an immune response to it. This could result in a condition known as serum sickness.

We will come back to passive immunity because the presence of passively acquired antibody may reduce the effectiveness of injected live virus vaccines.

Let's talk next about how vaccines produce active immunity. You will recall that active immunity is induced by infection with the disease-causing form of viruses and bacteria. With vaccines, we attempt to simulate that process, but without actually producing the disease, and without producing the complications that may accompany the disease.

At present there are two basic types of vaccines -- **live attenuated vaccines**, which must replicate inside the body in order to be effective, and **inactivated vaccines**, which cannot replicate. There are subtypes of both. Among live attenuated vaccines, **live viral** vaccines predominate. There are a couple of **live bacterial** vaccines, but these are rarely used in the U.S.

There are two main groups of inactivated vaccines, those that contain inactivated **whole virus** or **whole bacteria**, and a large second group, which we will refer to as **fractional vaccines**. These vaccines contain only immunogenic pieces of the organism of interest. Among the fractional vaccines, most are **protein-based**, such as subunit vaccines and toxoids. Some fractional vaccines are

polysaccharide-based, and may be either pure polysaccharide or conjugated polysaccharide.

In order to simplify some of the principles of vaccination, we have developed a few general rules. You will find these general rules in little boxes in your text. Here is the first General Rule: t**he more similar a vaccine is to the natural disease, the better the immune response to the vaccine**. This makes sense, since disease induced immunity is generally solid and long lasting, and the closer we can approximate that with vaccine, the better the protection from the vaccine. From this rule you would expect that live vaccines would have some advantages, since infectious diseases are caused by live organisms. To illustrate how live vaccines work, here is our third animation.

The events which produce immunity to a live attenuated vaccine are almost identical to those which lead to immunity following natural infection. The two main differences are that exposure is intentional, usually through injection of the virus. And that the virus is attenuated or weakened, so as not to cause illness. Since the person is not immune, the vaccine virus is able to replicate, and spreads throughout the body. The vaccine virus is very similar to natural disease virus so the immune system cannot tell them apart. As with natural infection, the vaccine virus is captured by a macrophage. The macrophage disassembles the virus, and presents viral antigens on its surface. The viral antigens are recognized by a T-cell in yellow and B-cell in blue. The T-cell signals the B-cell to activate. The activated B-cells begin to divide, producing millions of identical daughter B-cells. These B-cells then produce antibody directed against the vaccine virus. As with natural infection, the antibody attaches to the vaccine virus and destroys it, leading to elimination of the virus from the body. The antibody produced in response to the vaccine virus infection will persist for many years after the vaccine virus has been eliminated. Because the antibody cannot distinguish between vaccine virus and disease virus, the person is now immune to infection with a disease-causing form of the organism. So if months or years later an exposure to disease virus occurs, the antibodies will attack and kill it. No disease will result from the exposure.

As you can see, the immune response to a live vaccine is very similar to natural, or disease acquired immunity. In both situations, the vaccine agent replicates until an immune response is generated, which eliminates the invading pathogen. We will be mostly talking about live VIRUS vaccines, since we rarely use live bacterial vaccines in the United States.

There are several characteristics of live vaccines of which you should be aware. Live vaccines are an **attenuated, or weakened, form of the wild virus or bacteria**. WILD is a jargon term for the form of the virus or bacteria which causes the disease. For example, measles vaccine that you use every day originally caused measles DISEASE in a child in 1954. It took 9 years to transform wild measles virus into a mild mannered vaccine virus in a laboratory. Live vaccines **must replicate to be effective** and to produce an immune response. That's how they work. Anything that interferes with replication can decrease or

eliminate its ability to produce immunity. The immune response to a live vaccine is very **similar to that which occurs following natural illness**, or infection with the disease causing form of the organism. The mechanism is the same in both cases: the virus or bacteria replicates until an immune response stops it from replicating. As a result, live vaccines are usually, but not always, **effective with just one dose**.

Because they replicate, **severe reactions** are possible if the immune system cannot eliminate the vaccine organism. Fortunately, these severe reactions are rare, and occur mainly when live vaccines are given to immunodeficient persons. An important limitation of some live vaccines, particularly measles vaccine, is **interference from circulating antibody.** Antibody against the vaccine virus can reduce or eliminate the ability of the live vaccine agent to replicate. And if live vaccines do not replicate they do not work. Interference by circulating antibody appears to be a problem only with injected live virus vaccines. Finally, live vaccines are relatively **unstable,** and have very stringent storage and handling requirements. The virus in that little vial has to be kept viable. If the live agent is dead when you give it, it cannot replicate and it will not be effective.

We use several live attenuated vaccines in the United States. Here is a list of them. The live viral vaccines are **measles, mumps, and rubella**, which are usually given as combined MMR vaccine, **varicella, yellow fever, live attenuated influenza, and vaccinia**, or smallpox vaccine. Oral polio vaccine and rotavirus vaccines also contain live viruses, but neither of these vaccines are currently available in the United States. There are two live bacterial vaccines - **BCG** and **oral typhoid**. BCG is one of the most commonly used vaccines in the world. It is used for the prevention of tuberculosis. Most of you will never administer a dose of BCG vaccine, since there are few indications for it in the United States. But most of you have seen the results of BCG vaccination – the scars on the arms of children from other countries. Those scars are from BCG, not from smallpox vaccine.

Most of you will not use oral typhoid vaccine either, since it is used almost exclusively among international travelers and the military.

So that is the story with live vaccines. The second major vaccine category is inactivated vaccine. The antigen in inactivated vaccine is not alive, but it interacts with the immune system in a way similar to live vaccines. To illustrate how inactivated vaccines work, we would like to show you our last animation.

The events which produce immunity to inactivated vaccine are similar to those leading to immunity following natural infection or vaccination with live attenuated vaccine. The person is injected with inactivated antigen, which can be a whole inactivated virus or bacteria, or parts of either. Since the antigen is dead, it cannot reproduce. Therefore, large quantities of vaccine antigen must be injected to stimulate an immune response. As with natural infection or vaccination with live vaccines, the inactivated antigen is captured and ingested by macrophages. Antigens are presented on its surface. These antigens are recognized by a T-cell

and a B-cell. The T-cell signals the B-cell to activate. The B-cells divide, just as they do after natural infection or live attenuated vaccine. Then produce antibody directed against the vaccine antigen. Antibody attaches to the vaccine antigen, leading to its elimination from the body. Unlike natural infection or vaccination with live vaccines, a single dose usually does not confer immunity. Only a small amount of antibody is produced, and it may wane quickly. Additional doses are needed to boost the immune response. A second dose of antigen usually given within two months of the first causes a similar response. More antibody is produced, which attaches to and eliminates the vaccine antigen. This time, more antibody remains but long-lasting immunity still may not be conferred. At least one additional booster shot is usually required to bring the antibodies up to a protective level, but even this protection can gradually wane over time. An additional booster dose may be needed years after the primary series to ensure that the antibody level remains protective. While antibodies remain in body, the person is immune to the disease-causing form of the virus or bacteria. If an exposure to the disease organism occurs, the antibodies will attack it. Usually there is no disease from the exposure, or if disease does occur, it is milder.

I hope you noticed the similarity between the mechanism of inactivated vaccination and live vaccination. The basic immune response process is the same. The main difference is that live antigens replicate until the immune system stops them. Inactivated agents cannot replicate, so the immune system must usually be exposed to the antigen several times in order to produce immunity. Here are some other characteristics of inactivated vaccines. Inactivated vaccines are not alive, so they **cannot replicate** and are noninfectious. Because they are noninfectious, they can be used in immunodeficient people. In general, inactivated vaccines are **not as effective** as live attenuated vaccines, meaning that estimates of vaccine efficacy are usually lower than with live vaccines. One way that circulating antibody eliminates infectious agents is to interfere with replication. Since inactivated vaccines do not replicate, there is **minimal interference** from circulating antibody. This means you can give inactivated vaccines in the presence of passive antibody, such as maternal antibody, so you can give them earlier in life. In fact, it is common to give inactivated vaccine and antibody at the same time. For instance, an infant born to a woman who is a hepatitis B carrier receives hepatitis B immune globulin in one leg and hepatitis B vaccine in the other leg. The same thing happens for postexposure rabies prophylaxis.

Another difference between live and inactivated vaccines is that live vaccines generally produce immunity with a single dose. Inactivated vaccines **generally require 3 to 5 doses**. The first dose usually does not provide much protection. It is a primer for the immune system. The subsequent 2 or 3 doses provide protection by increasing antibody levels. The **immune response to an inactivated vaccine is mostly humoral**, unlike live vaccines which produce both humoral and cellular immunity. Unlike live vaccines, in which immunity is generally long lasting, the **antibody titer following an inactivated vaccine may fall**, and may in some cases fall below a protective level. It is not known why live vaccines produce such good long term immunologic memory, and inactivated agents generally do not. In any case, if antibody wanes to nonprotective levels, it

may be necessary to give the immune system a little reminder, in the form of a booster dose of vaccine. At present, tetanus and diphtheria toxoids are the only routine vaccines that require booster doses to maintain protection in healthy people.

Inactivated whole virus vaccines available in the U.S. include **inactivated polio, rabies, and hepatitis A vaccines**. Inactivated whole bacterial vaccines include the old **pertussis vaccine, killed typhoid, cholera, and plague** vaccines. These vaccines are now only of historical interest, since none of them – including cholera vaccine -- are available in this country. Here's a list of fractional vaccines, which contain only parts of a virus or bacteria. Subunit vaccines include **hepatitis B, influenza**, **acellular pertussis**, **typhoid Vi**, and **Lyme disease** vaccines. Lyme disease vaccine is no longer available in the United States. **Anthrax** is also a subunit vaccine. There are two toxoids, which are inactivated toxins of **diphtheria** and **tetanus**. Acellular pertussis vaccines could be classified as toxoids as well. We will talk about pertussis vaccines in the second session of the course.

Another type of fractional vaccine is composed of polysaccharide, either alone or conjugated to a protein carrier. Pure polysaccharide vaccines include **pneumococcal and meningococcal** vaccines. **Pneumococcal** vaccine is also available as a protein conjugate, which is given to children. All ***Haemophilus influenzae*** **type b** vaccines are conjugated to protein as well. Polysaccharides are complex sugars that make up the outer coat of certain bacteria, most notably the streptococcus, Neisseria, and Hemophilus families. The polysaccharide coat is important in the development of disease and immunity. So vaccine production should be fairly straight forward. Just purify the polysaccharide and put it in a vial. That is how it is usually done – but there is a catch.

Most polysaccharides are what are called T independent antigens. You will recall from the animations that the T cell is very important in the development of immunity. Polysaccharides are capable of stimulating the B cell directly, without the help of a T cell. This may seem like a good thing, but it is not. Polysaccharides are not very good antigens. Most importantly, polysaccharide vaccines are **not consistently immunogenic in children younger than two years of age**. This is a serious shortcoming if the disease you want to prevent occurs commonly in infants, like Hib and pneumococcal disease. In addition to this lack of effect in infants, polysaccharide vaccines do not reliably produce a **booster response**. That means that the amount of antibody produced does not increase substantially following subsequent doses. This is the reason the recommendations for revaccination with pneumococcal and meningococcal vaccines are a bit vague. Repeated doses result in little or no additional protection. Another limitation of polysaccharide vaccines is that they produce antibody with **less functional activity**. Much of the antibody produced is IgM, instead of IgG. The good news is that the limitations of pure polysaccharide vaccines can be remedied. The immunogenicity of these vaccines is improved by **conjugation**, literally a joining of polysaccharide with protein. The resulting conjugated material is a T dependent antigen, and doesn't have the limitations of

a T independent antigen. Most importantly, conjugates are effective in infants. We will discuss pneumococcal and Hib conjugate vaccines in more detail in the second session of the course.

So, now you know the basic characteristics of vaccines and how they work. We will revisit these themes again as we discuss the specific vaccines.